The Effect of Variable vs Fixed Feeding on Glycaemic Control in the Adult ICU: Virtual Trial Evaluation

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Abstract: Elevated blood glucose (BG) concentrations (Hyperglycaemia) is a common complication in the adult intensive care unit (ICU), and is associated with increased morbidity and mortality. However, it has been shown that effective glycaemic control (GC) can reduce morbidity and mortality. STAR is a model-based GC protocol that uniquely maintains normal BG by changing both insulin and nutrition interventions, and has been proven to be effective in controlling BG levels in the ICU. However, most GC protocols in the ICU only change insulin interventions, making the variable feed aspect of STAR less clinically desirable. This paper investigates two simpler feeding protocols as an alternative. Fixed feed (100% calorific goal) and stepped feed (60%, 80% and 100% calorific goal for the first 3 days of GC, and then 100% thereafter) protocols, in conjunction with the STAR protocol, are simulated with clinically validated virtual trials on a 221 virtual patient cohort. The GC safety, performance and workload is compared for each of the different feeding protocols. The variable and stepped feeding protocol achieved very similar GC performance and safety, with a per-patient median time in the targeted 4.4-8.0 mmol/L BG range of 89.0% vs. 88.3% respectively and the number of patients BG < 4.0 mmol/L being 77 vs. 78 respectively. In contrast, the fixed feeding protocol resulted in significantly poorer GC performance with 85.6% time in the targeted 4.4-8.0 mmol/L band ($P<0.025$). Both the fixed and stepped feeding protocols significantly reduced the number of feed changes required per day (6.4 variable vs. 0 fixed and 0.5 stepped, $P<0.025$). However, as a consequence a small increase in the number of BG measurements per day was seen (11.4 variable vs. 13.4 fixed vs. 12 stepped, $P<0.025$). Overall the stepped feeding protocol provides a simple alternative to the current variable feeding protocol, with similar GC safety and performance.

Keywords: Decision support and control; Healthcare management, disease control, critical care; Biomedical system modelling, simulation and visualization.

1. INTRODUCTION

In the ICU a patient's body is under considerable amount of stress, which results in dysregulation of blood glucose (BG) levels (Clutter *et al.*, 1980) and ultimately hyperglycaemia (elevated BG levels) (Shamoon, Hendler and Sherwin, 1981; McCowen, Malhotra and Bistrian, 2001). Hyperglycaemia in the ICU has been shown to be associated with increased morbidity and mortality (Capes *et al.*, 2000; Mizock, 2001; Krinsley, 2003). Variability in BG levels, and thus poor control, has also been in shown to be independently associated with mortality (Egi *et al.*, 2006; Krinsley, 2008; Lanspa *et al.*, 2014).

It has however been shown that effective glycaemic control (GC) can reduce mortality and morbidity (Van den Berghe *et al.*, 2001; Finney *et al.*, 2003; Krinsley, 2004; Chase *et al.*, 2008), organ failure (Chase, Pretty, *et al.*, 2010) and cost of care (Krinsley and Jones, 2006; Van den Berghe *et al.*, 2006). However, due to inter- and intra- patient variability, some GC protocols have increased hypoglycaemia, associated with increased mortality (Bagshaw *et al.*, 2009; Egi *et al.*, 2010; Finfer *et al.*, 2012), overall providing inconsistent safe and effective GC.

A GC protocol that has proven to be effective is the model-based STAR (Stochastic TARgeted) protocol (Fisk *et al.*, 2012; Stewart *et al.*, 2016). STAR uses a physiological insulin-glucose model (Lin *et al.*, 2011; Stewart *et al.*, 2015) in conjunction with a stochastic model of variability (Lin *et al.*, 2006), to estimate a patient's current metabolic state, and potential future variability. Thus, treatments are selected by forward simulation and desired risk of moderate hypoglycaemia (BG < 4.4 mmol/L).

The STAR GC protocol maintains normal BG levels by changing both insulin and nutrition interventions given to the patient (Fisk *et al.*, 2012). However, the majority of GC protocols used in the ICU only change insulin interventions, making STAR unique and less clinically desirable in this respect. Thus, simplifying the STAR GC protocol by simplifying the protocol in which feed is given to the patient may increase compliance and clinical utilization of the protocol.

This paper uses virtual trials to compare the GC performance of the STAR protocol with variable feed, fixed feed and stepped feed.

2. METHODS

2.1 Patient Data and Virtual trials

Clinical data from 221 patients, treated with the STAR protocol (2011-2015) (Stewart *et al.*, 2016), in Christchurch Hospital ICU was used to generate virtual patients. The Upper South Regional Ethics Committee, New Zealand, granted approval for the audit, analysis and publication of this data. The cohort demographics can be seen in Table 1.

Virtual patients are created by fitting the time varying model-based patient-specific, insulin sensitivity parameter to the patient's clinical data. This model-based insulin sensitivity is a critical marker of a patient's metabolic state (Chase *et al.*, 2007; Pretty *et al.*, 2012). The insulin sensitivity profile is then used with a GC protocol to simulate the BG response, as done previously (Chase, Suhaimi, *et al.*, 2010; Dickson *et al.*, 2016).

2.2 Feeding protocols

In the Christchurch Hospital ICU, at the beginning of a patients stay, a calorific goal feed is determined based on ACCP Guidelines ('American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis', 1992), see Table 2 and Equation 1. This calorific goal and the specific feed content given determines the target feed rate for the patient.

Table 2: Coefficients used to determine an ICU patients daily calorific goal in Christchurch ICU Hospital.

Frame Size (F)	Small	Average		Big
	0.9	1.0		1.1
Age (A)	≤39	40-59	60-79	≥80
	1.1	1.0	0.9	0.8
Gender (G)	Male		Female	
	1.0		0.8	

$$A * \mathrm{F} * G * 2000 = Calorific\ Goal/Day \quad (1)$$

The virtual patient cohort is simulated on 3 different feeding protocols:

- Variable feed rate (Current method), the STAR GC protocol chooses the appropriate feed rate at each BG measurement, which ensures the patient safety and normal glycaemia (Fisk *et al.*, 2012). The GC protocol can change the feed rate by +/- 30% calorific at each BG measurement and range from 30-100% calorific goal.
- Fixed feed rate (100% calorific goal).
- Stepped feed rate (60%, 80% and 100% calorific goal for the first 3 days of GC, and then 100% thereafter). The stepped feeding protocol is based on what is achieved in the best ICU unit in the Cahill et al. 2010 study (Cahill *et al.*, 2010), as seen in Figure 1.

Table 1: STAR virtual cohort patient demographics (Rounded to 1dp where appropriate).

Number of Patients	221
Number Hours	21,892
Age	64.0 [54.0 - 72.0]
Gender (% Male)	66.1
ICU length of stay	8.4 [3.1 - 15.3]
Days on Protocol	2.7 [1.5 - 5.7]
Operative (%)	29.0
APACHE II Score	21.0 [16.0 - 27.0]
ICU Mortality (%)	28.0

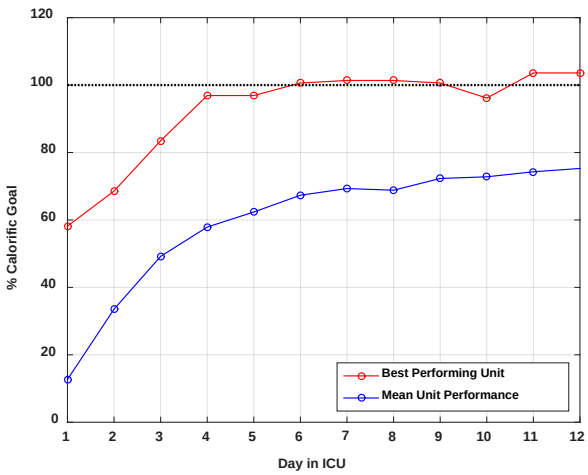

Figure 1: Results of Cahill et al. 2010 study, reviewing the calorific goal feed achieved across multiple units. Data adapted from (Cahill *et al.*, 2010).

When simulating the fixed and stepped feeding protocol the STAR GC protocol is only able to change insulin interventions. For all protocol simulations the low carbohydrate enteral feed Glucerna 1.0 Cal (Abbott Nutrition, Columbus, Ohio, USA) is used, as this is the most commonly used feed in the Christchurch Hospital ICU.

2.3 Analysis and Statistics

The GC achieved with STAR and the different feeding protocols are compared in terms of safety (number patients BG < 4.0 mmol/L), performance (percentage of time BG 4.4 -8.0 mmol/L and BG > 10 mmol/L) and workload (Number of insulin and feed changes, and number of BG measurements per day). Performance and workload are assessed on a per-patient basis.

BG measurements are linearly interpolated and resampled hourly to estimate BG levels between measurements. This allows fairer comparison of BG statistics when the measurement intervals are variable. P-values were computed using the Mann-Whitney rank-sum test for all continuous data and the chi-squared test for categorical data. P-values <0.025 are considered statistically significant (After Bonferroni correction) (Bonferroni, 1936).

3. RESULTS

The virtual trial GC performance results for STAR, with each of the feeding protocols, can be seen in Table 3. It can be seen that using a variable feeding regime as opposed to a fixed feeding regime significantly improves the GC performance, but has a high number of feed changes associated with it. However, using a stepped feeding regime may offer a simpler, lower workload protocol, with similar GC performance to the variable feed protocol.

Table 3: Comparison of the virtual trial GC performance results for the 3 feeding protocols. Data shown as: Median [Inter-Quartile Range] where appropriate.

Feeding Protocol	***Variable***	***Fixed***	***Stepped***	***P-Values***	
				Var vs. Fixed	Var vs. Stepped
GC Performance					
Num. patients BG < 4.0 mmol/L	77	82	78	0.71	1.00
Num. patients BG < 2.22 mmol/L	9	10	11	1.00	0.82
Per-patient Resampled Hourly BG Statistics					
BG median (mmol/L)	6.2 [6.0 - 6.7]	6.3 [6.0 - 6.9]	6.3 [6.0 - 6.7]	0.24	0.89
BG mean (mmol/L):	6.4 [6.20 - 6.9]	6.5 [6.2 - 7.2]	6.4 [6.2 - 6.9]	0.17	0.75
BG Std Dev (mmol/L):	1.2 [0.87 - 1.7]	1.3 [0.9 - 1.9]	1.2 [0.9 - 1.7]	0.05	0.89
% BG < 2.22 mmol/L	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.81	0.65
%BG < 4.4 mmol/L	0.0 [0.0 - 3.6]	0.0 [0.0 – 4.0]	0.0 [0.0 - 3.8]	0.80	0.90
%BG 4.4-8.0 mmol/L	89.0 [75.8 - 94.7]	85.6 [68.8 - 94.4]	88.3 [76.2 - 95.7]	<0.025	0.88
%BG > 10.0 mmol/L	0.7 [0.0 - 5.3]	1.6 [0.0 - 7.1]	0.6 [0.0 - 5.6]	0.07	0.93
Workload					
Num. Measurements	10237	12060	1196	-	-
Num. insulin changes	6759	6964	6626	-	-
Num. zero insulin	1472	1372	1494	-	-
Num. feed changes	5270	0	370	-	-
Per-patient Treatment Statistics					
Num. Measures/day:	11.4 [10.1 - 13.7]	13.4 [11.6 - 16.8]	12.0 [10.6 - 14.7]	<0.025	<0.025
Num. insulin changes/day	7.5 [6.4 - 8.3]	7.8 [6.5 - 8.9]	7.4 [6.0 - 8.4]	0.03	0.31
Num. zero insulin/day:	0.9 [0.0 - 2.8]	0.9 [0.0 - 2.7]	1.1 [0.0 - 3.2]	0.50	0.61
Num. feed changes/day:	6.4 [4.4 - 8.0]	0.0 [0.0 - 0.0]	0.5 [0.2 - 0.7]	<0.025	<0.025

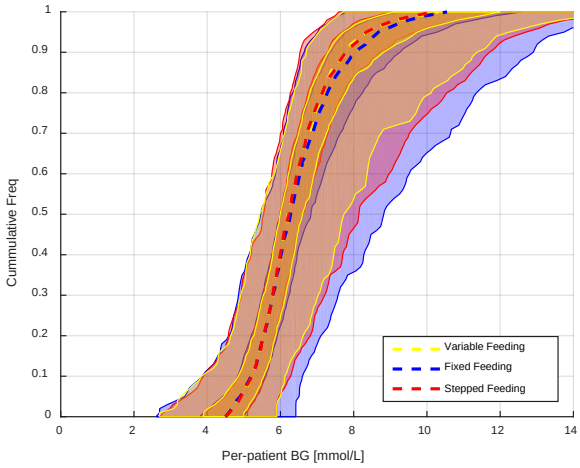

Figure 2: Per-patient blood glucose (BG) cumulative distribution range for each feeding protocol. Light shaded region showing 5th-95th percentile, Dark shaded region showing 25th-75th percentile. Dashed line showing median value.

Figure 2 shows how the spread of BG measurements per-patient is effected by the different feeding protocols. This figure shows that majority of the GC performance can be captured with either a fixed or stepped feeding protocol.

4. DISCUSSION

4.1 Variable vs. Fixed

From the results it can be seen that the safety of the variable feed protocol was slightly safer than the fixed feed protocol, having 5 less patients experiencing mild hypoglycaemia (77 vs. 82 patients BG < 4.0 mmol/L, P = 0.71 Table 3). However, a significant benefit in GC performance is achieved by placing patients on a variable feeding protocol as opposed to a fixed feed protocol (Per-patient median time BG in 4.4-8.0 mmol/L 89.0% vs 85.6%, P < 0.025 Table 3). In Figure 2 it can be seen that the percentiles per-patient BG are almost identical between the variable and fixed feeding protocols, with the

largest discrepancies being at the 75th and 95th percentiles. Thus showing that the fixed feed protocol lost a significant amount of its GC performance from being unable to effectively lower a specific proportion of patient's high BG levels. Overall showing that a significant decrease in GC performance and slight decrease in safety is achieved by using a fixed feeding protocol.

Between the protocols the workload is significantly different in terms of the number of BG measurements per day (Median per-patient 11.4 vs 13.4, P<0.025 Table 3). However, the number of insulin changes per day were similar (Median per-patient 7.5 vs 7.8, P=0.03 Table 3) and inherently the fixed feed protocol had no feed changes per day compared to the variable feed protocol, which had a median of 6.4 (P < 0.025, Table 3). Therefore, showing that the variable feeding protocol was able to more efficiently control the cohort. This may be due to the modification of both feed and insulin more effectively lowering a patients high BG (BG >10 mmol/L), compared to the fixed feed protocol which may have a patients insulin dose already maximised.

4.2 Variable vs. Stepped

It can be seen that the safety of the variable and stepped feed protocols are very similar, having 77 and 78 patients BG < 4.0 mmol/L (P = 1.00, Table 3). However, the variable feeding protocol can be seen to be slightly safer in having 3 less cases of the patients BG < 2.22 mmol/L (P=0.82), Table 3. This may be due to the variable feeding protocol having more flexibility and being able to feed lower resulting in lower insulin treatments, thus minimising the impact of any large changes in a patients insulin sensitivity over there first few days of stay (Pretty *et al.*, 2012). The GC performance achieved between the variable and stepped feeding protocols is similar (Per-patient median time BG in 4.4-8.0 mmol/L 89.0% vs 88.3%, P=0.88 Table 3). In addition, from Figure 2 it can be seen that the percentiles per-patient BG are almost identical between the variable and stepped feeding protocols, with only small discrepancies at the 75th and 95th percentiles. Therefore showing that a similar GC performance and safety can be achieved with simpler stepped feeding protocol.

Between the two protocols, the workload appears to be slightly more for the stepped feeding protocol in terms of number of measurements per day (Median per-patient 11.4 vs 12.0 P<0.025, Table 3). However, the number of insulin changes per day were similar (Median per-patient 7.5 vs 7.4, P=0.31 Table 3) and the stepped feed protocol had significantly less feed changes per day compared to the variable feed protocol (Median per-patient 6.4 vs 0.5 P<0.025, Table 3). Therefore, showing that the stepped feeding protocol was able to significantly reduce the number of feed changes per day for only a slight increase in the number of BG measurements per day. Again, this is most likely due to patients being most variable over the first few days of stay (Pretty *et al.*, 2012), and therefore lower feed treatments resulting in lower insulin treatments, minimising the impact of any metabolic variability.

4.3 Clinical acceptability

The majority of other published GC protocols don't not control feed and thus don't explicitly publish in terms of percentage of targeted feed given to a patient, making comparisons of feeding performance difficult. However, the number measurements required per day and GC performance achieved by all of the feeding protocols is very similar to that seen in other recent ICU GC protocols (Chase *et al.*, 2008; Amrein *et al.*, 2012; Van Herpe *et al.*, 2013). Thus making any of the feeding protocols proposed suitable for use in the ICU.

Both of the alternative feeding protocols significantly reduce the number of feed changes required per day compared to the current variable feeding protocol. In addition, both of these protocols also increase the number of measurements needed per day to maintain GC. However, of the two protocols the stepped feeding protocol resulted in the most similar GC performance and safety to the variable feeding protocol, with the added benefit of a significant reduction in the number of feed changes and the minor implication of 0.6 more measurements required per day. Moreover, the stepped feeding protocol also fed better than the best reported unit published in Cahill et al. 2010. Thus the safe, simple and low workload stepped feeding protocol is the best choice from all of the feeding protocols investigated.

4.4 Limitations

The stepped feeding protocol is based on the results of the Cahill et al. 2010 study (Cahill *et al.*, 2010), Figure 1, which reviews, the mean percentage of calorific goal fed achieved during the first few days of ICU stay, in multiple ICUs. Although GC is commonly started at the start of a patients stay in the ICU, this may not always be the case. Therefore, if the stepped feeding protocol is used, it may result in feeding patients less than observed in the best practice in Cahill et al. 2010 (Cahill *et al.*, 2010).

The STAR GC protocol, uses model-based, patient-specific control in conjunction with a stochastic model to predict the best treatment for a patient. Therefore irrespective of the feeding protocol STAR is able to achieve very good GC. However, small benefits may be achieved by changing the feeding protocol used. The simple stepped feeding protocol, achieves a similar GC performance, with a significant reduction in the number of feed changes required per patient. Therefore, the results of these virtual trials suggest that a clinical pilot trial is needed to validate these results on real patients, prior to full clinical implementation.

5. CONCLUSIONS

Three different feeding protocols were simulated with the STAR GC protocol, using the previously published virtual trial approach. Each of the feeding protocols have varying degrees of simplicity and clinical acceptability. A significant reduction in GC performance was found when using the fixed feeding protocol compared to the other feeding protocols (89.0%

variable vs. 85.6% fixed vs. 88.3% stepped, time in 4.4-8.0 mmol/L). A significant reduction in the number of feed changes was achieved by using the stepped feeding protocol compared to the variable feeding protocol (6.4 vs 0.5 feed changes/day per-patient), with the minor implication of 0.6 more measurements required per day. Overall the stepped feeding protocol is a simple alternative to the current variable feeding protocol which provides similar GC safety and performance. Thus the stepped feeding protocol could be adapted by STAR to allow it to be more clinically acceptable GC protocol in current or new ICUs.

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